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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,860	04/13/2004	Koichi Matsuzaki	040176	2658

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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/822,860	MATSUZAKI ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-12 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, drawn to a polyclonal antibody specific for a phosphorylated linker region in Smad 2, classified in class 530, subclass 387.7.

It is noted for Applicant's convenience that this is a requirement for the election of a Group for examination NOT a requirement for an election of species because although the claims are presented in Markush format, the claims are drawn multiple agents which do not share, as a whole, a substantial structural feature disclosed as being essential to their utility. Thus, the analysis of the claims, for restriction purposes, is subject to the findings of the court wherein the court found that unity of invention exists where entities included within a Markush group share a substantial structural feature disclosed as being essential to utility of the invention, In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Since the members of the group do not share a substantial structural feature disclosed as being essential to utility of the invention, the group as claimed fails the Harnisch test and the claims are not accorded Markush restriction practice because they do not meet the requirements to be accorded Markush practice under MPEE 803.02.

II. Claim1-5, drawn to a polyclonal antibody specific for a phosphorylated linker region in Smad 3, classified in class 530, subclass 387.7.

It is noted for Applicant's convenience that this is a requirement for the election of a Group for examination NOT a requirement for an election of species because although the claims are presented in Markush format, the claims are drawn multiple agents which do not share, as a whole, a substantial structural feature disclosed as being essential to their utility. Thus, the analysis of the claims, for restriction purposes, is subject to the findings of the court wherein the court found that unity of invention exists where entities included within a Markush group share a substantial structural feature disclosed as being essential to utility of the invention, In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Since the members of the group do not share a substantial structural feature disclosed as being essential to utility of the invention, the group as claimed fails the Harnisch test and the claims are not accorded Markush restriction practice because they do not meet the requirements to be accorded Markush practice under MPEE 803.02.

III Claim1-5, drawn to a polyclonal antibody specific for a phosphorylated linker region in Smad 2 and Smad 3, classified in class 530, subclass 387.7.

It is noted for Applicant's convenience that this is a requirement for the election of a Group for examination NOT a requirement for an election of species because although the claims are presented in Markush format, the claims are drawn multiple agents which do not share, as a whole, a substantial structural feature disclosed as being essential to their utility. Thus, the analysis of the claims, for restriction purposes, is subject to the findings of the court wherein the court found that unity of invention exists where entities included within a Markush group share a substantial structural feature disclosed as being essential to utility of the invention, In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Since the members of the group do not share a substantial structural feature disclosed as being essential to utility of the invention, the group as claimed fails the Harnisch test and the claims are not accorded Markush restriction practice because they do not meet the requirements to be accorded Markush practice under MPEE 803.02.

IV. Claims 6-8, drawn to a method of screening drugs that inhibit phosphorylation of the linker region in Smad 2, classified in class 435, subclass 7.1.

V. Claims 6-8, drawn to a method of screening drugs that inhibit phosphorylation of the linker region in Smad 3, classified in class 435, subclass 7.1.

VI. Claim 9, drawn to a method of screening drugs that inhibit phosphorylation of a Smad protein, including the steps of: (i) bringing a Smad proteins, as a substrates, into contact with a candidate drug; (ii) reacting said Smad proteins with active p38 in the presence of ATP; and (iii) detecting phosphorylated Smad proteins in the reacted Smad proteins to evaluate the inhibition of phosphorylation; classified in class 435, subclass 4.

VII. Claim 10, drawn to a method of screening drugs that inhibit phosphorylation of a Smad protein, including the steps of: (i) stimulating arbitrary cells with TGF-β

and recovering the cells after a predetermined time; (ii) immunoprecipitating a homogenate of the recovered cells with an antibody(ties) specific for a kinase (iii) incubating the immnoprecipitated samples, a candidate drug(s) recombinant Smad2 and phosphorylating Smad2 in vitro; and (iv) detecting a phosphorylated Smad proteins) in the reacted Smad proteins by immunoblotting technique using an antibody(ties) against phosphorylation in the linker region to evaluate the inhibition of phosphorylation, classified in class 435, subclass 7.1.

VIII. Claim 11, drawn to a method for assessing the activity of fibrosis stimulating signal in hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad2 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

IX. Claim11, drawn to a method for assessing the activity of fibrosis stimulating signal in hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad3 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

X. Claim11, drawn to a method for assessing the activity of fibrosis stimulating signal in hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad 2 and Smad 3 is incubated with a sample of object tissue, classified in class 435, subclass 7.1

.XI. Claim 11, drawn to a method for assessing the efficacy of the molecular targeting therapy for hepatic fibrosis in which the polyclonal antibody specific for a

phosphorylated linker region in Smad2 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

XII. Claim11, drawn to a method for assessing the efficacy of the molecular targeting therapy for hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad3 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

XIII. Claim11, drawn to a method for assessing the efficacy of the molecular targeting therapy for hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad 2 and Smad3 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

XIV. Claim 12, drawn to a method for assessing the activity of oncogenesis stimulating signal in human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad2 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

XV. Claim12, drawn to a method for assessing the activity of oncogenesis stimulating signal in human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad3 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

XVI. Claim12, drawn to a method for assessing the activity of oncogenesis stimulating signal in human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad 2 and Smad3 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

XVII. Claim 12, drawn to a method for assessing the efficacy of the molecular targeting therapy for human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad2 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

XVIII. Claim12, drawn to a method for assessing the efficacy of the molecular targeting therapy for human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad3 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

XIX. Claim12, drawn to a method for assessing the efficacy of the molecular targeting therapy for human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad 2 and Smad3 is incubated with a sample of object tissue, classified in class 435, subclass 7.1.

It is noted for Applicant's convenience that the election requirement for Inventions VIII-XIX is an election of a Group for examination NOT a requirement for an election of species because although the claims are presented in Markush format, the claims are drawn multiple methods using multiple agents which do not share, as a whole, a substantial structural feature disclosed as being essential to their utility. Thus, the analysis of the claims, for restriction purposes, is subject to the findings of the court wherein the court found that unity of invention exists where entities included within a Markush group share a substantial structural feature disclosed as being essential to utility of the invention, In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Since the members of the group do not share a substantial structural feature disclosed as being essential to utility of the invention, the group as claimed fails the Harnisch test and the claims are not accorded Markush restriction practice because they do not meet the requirements to be accorded Markush practice under MPEE 803.02.

The inventions are distinct, each from the other because of the following reasons:

Inventions I-III are directed to related antibodies. The related inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j).

In the instant case, the inventions are distinct because the biological process involved in antibody generation is variable and unpredictable in nature. It is the structural differences generated by these processes that allow the antibodies to recognize different epitopes. It is unlikely that any two antibodies, even those directed to the same epitope, have the same structure. Thus, Inventions I-III are distinct. Since the products are unrelated searching all of the claims of both groups would invoke a burdensome search.

Inventions I-III and IV-XIX are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the antibodies could be used in immunoaffinity chromatography.

Inventions IV-XIX are directed to related methods. The related inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j).

In the instant case, the inventions are related in that they all detect the phosphorylation state of a Smad protein as part of the method. Inventions IV-XIX are distinct each from the other in they have different steps, objectives, and/or combinations thereof. Invention IV is distinct in that it screens for drugs that inhibit the phosphorylation of the linker region in Smad2. Invention V is distinct in that it screens for drugs that inhibit the phosphorylation of the linker region in Smad3. Invention VI is a distinct method of screening drugs that inhibit phosphorylation of a Smad protein(s), including the steps of: (i) bringing a Smad protein(s), as a substrate, into contact with a candidate drug; (ii) reacting said Smad protein(s) with active p38 in the presence of ATP; and (iii) detecting phosphorylated Smad protein(s) in the reacted Smad protein(s) to evaluate the inhibition of phosphorylation. Invention VII is a distinct method of screening drugs that inhibit phosphorylation of a Smad protein, including the steps of: (i) stimulating arbitrary cells with TGF-β and recovering the cells after a predetermined time; (ii) immunoprecipitating a homogenate of the recovered cells with an antibody(ties) specific for a kinase (iii) incubating the immunoprecipitated samples, a candidate drug(s) recombinant Smad2 and phosphorylating Smad2 in vitro; and (iv) detecting a phosphorylated Smad protein(s) in the reacted Smad proteins by immunoblotting technique using an antibody(ties) against phosphorylation in the linker region to evaluate the inhibition of phosphorylation. Invention VIII is a distinct method for assessing the activity of fibrosis stimulating signal in hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad2 is incubated with a sample of object tissue. Invention IX is a distinct method for assessing the activity of fibrosis stimulating signal in hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad3 is incubated with a sample of object tissue. Invention X

is a distinct method for assessing the activity of fibrosis stimulating signal in hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad 2 and Smad3 is incubated with a sample of object tissue. Invention XI is a distinct method for assessing the efficacy of the molecular targeting therapy for hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad2 is incubated with a sample of object tissue. Invention XII is a distinct method drawn to a method for assessing the efficacy of the molecular targeting therapy for hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad3 is incubated with a sample of object tissue. Invention XIII is a distinct method drawn to a method for assessing the efficacy of the molecular targeting therapy for hepatic fibrosis in which the polyclonal antibody specific for a phosphorylated linker region in Smad 2 and Smad3 is incubated with a sample of object tissue. Invention XIV is a distinct method for assessing the activity of oncogenesis stimulating signal in human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad2 is incubated with a sample of object tissue. Invention XV is a distinct method for assessing the activity of oncogenesis stimulating signal in human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad3 is incubated with a sample of object tissue. Invention XVI is a distinct method for assessing the activity of oncogenesis stimulating signal in human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad 2 and Smad3 is incubated with a sample of object tissue. Invention XVII is a distinct method for assessing the efficacy of the molecular targeting therapy for human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad2 is incubated with a sample of object tissue. Invention XVIII is a distinct

method for assessing the efficacy of the molecular targeting therapy for human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad3 is incubated with a sample of object tissue. Invention XIX is a distinct method for assessing the efficacy of the molecular targeting therapy for human colon cancer in which the polyclonal antibody specific for a phosphorylated linker region in Smad 2 and Smad 3 is incubated with a sample of object tissue.

Furthermore, searching all of the inventions of Groups I-XIX would invoke a burdensome search. Some of the inventions have been classified separately. Thus, each of these inventions has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. Although some of the inventions are classified similarly, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search.

Because these inventions are distinct for the reasons given above and the search required for one group is not required for another group, restriction for examination purposes as indicated is proper.

Species Elections for Groups IV-VII

A. Claims 6, 7, 9, and 10 are generic to the following disclosed patentably distinct species for the location in which drug contacts its target:

1) *in vitro,* as contemplated in the specification

2) *in vivo,* as contemplated in the specification

B. Claims 7 and 10 are generic to the following disclosed patentably distinct species for the location in which cells are treated with TGF-β:

1) *in vitro,* as contemplated in the specification

2) *in vivo,* as contemplated in the specification

C. Claims 7 is generic to the following disclosed patentably distinct species for TGF-β: expression:

1) intrinsically expressed

2) overexpressed

D. Claim 7 is generic to the following disclosed patentably distinct species of drug:

1) anti-fibrosis drug

2) not an anti-fibrosis drug

E. Claims 9 and 10 are generic to the following disclosed patentably distinct species of Smad:

1) Smad 2, as contemplated in the specification

2) Smad 3, as contemplated in the specification

The above species are independent or distinct because they comprise structurally distinct molecules and/or have different modes of operation and different effects. Further, each species would require different searches and the consideration of different patentability issues.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species from each of group A-E for the elected Invention, even though this requirement is traversed. Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 of the other invention.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Note:

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims

> and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicant is advised that the reply to this restriction requirement to be complete must include an election of the invention to be examined even though the requirement is traversed (37 CFR 1.143).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR